CLAIMS

What is claimed is:

1. A process for preparing (+)-(2S,3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol in its free base, its salt, or both, which process comprises an enzyme-catalyzed dynamic kinetic resolution by equilibrating the two chiral centers of (+/-)-(2R*, 3R*)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol.

2. The process according to claim 1 which process comprises:

(1) dissolving (+/-)-(2R*, 3R*)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol in a solvent and water and adjusting the pH from about pH 1 to about pH 8;

(2) adding a catalytic amount of an esterase enzyme or a lipase enzyme optionally with stirring and optionally adjusting the pH from about pH 1 to about pH 8;

(3) adding seed crystals selected from the group consisting of (i) (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol free base, (ii) a salt of (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol, and (iii) a mixture of said free base and said salt of (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol, while maintaining the pH between about pH 1 and about pH 8 and the reaction temperature between about 10 C° and about 50°C;

(4) quenching the reaction with an organic solvent and a base;

(5) removing said esterase enzyme or said lipase enzyme from the reaction; and

(6) isolating (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol free base.

3. The process according to claim 2 further comprising the steps of:

(7) converting the (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol free base into a (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol salt; and

(8) recrystallizing said salt to produce a purer form of the (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol salt.

4. The process according to claim 3 wherein the salt is (+)-(2S, 3S)-2-(3 -chlorophenyl)-3,5,5-trimethyl-2-morpholinol hydrochloride salt.

5. The process according to claim 2 wherein the enzyme is an esterase enzyme.

6. The process according to claim 2 wherein the enzyme is a lipase enzyme.

7. The process according to claim 5 wherein the esterase enzyme is esterase from Thermoanaerobium brockii or esterase from Thermomyces lanugenosus.

8. The process according to claim 6 wherein the lipase enzyme is lipase from Pseudomonas fluorescens.

9. The process according to claim 2 wherein said pH from about pH 1 to about pH 8 is adjusted using (i) an acid, (ii) a base, or (iii) a combination of an acid and a base.

10. The process according to claim 9 wherein said acid used to adjust pH is an organic acid or an inorganic acid; and said base used to adjust pH is an organic base or an inorganic base.

11. The process according to claim 10 wherein said acid used to adjust pH is selected from the group consisting of hydrochloric acid, sulfuric acid, phosphoric acid, and acetic acid.

12. The process according to claim 10 wherein said base used to adjust pH is selected from the group consisting of an alkali metal hydrogen carbonate, an alkali metal carbonate, an alkali metal hydroxide, ammonium hydroxide, an aliphatic amine, and an aromatic amine.

13. The process according to claim 12 wherein the alkali metal hydrogen carbonate is selected from the group consisting of sodium hydrogen carbonate and potassium hydrogen carbonate; the alkali metal carbonate is selected from the group consisting of sodium carbonate and potassium carbonate; and the alkali metal hydroxide is selected from the group consisting of sodium hydroxide and potassium hydroxide.

14. The process according to claim 2 wherein the solvent is selected from the group consisting of a protic solvent, a ketonic solvent, and an ether solvent.

15. The process according to claim 14 wherein said solvent is selected from the group consisting methanol, ethanol, acetone, and tetrahydrofuran.

16. The process according to claim 2 wherein the seed crystal is (i) a (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol hydrochloride salt or (ii) a (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol hydrogen sulfate salt.

17. The process according to claim 2 wherein step (4) has a pH greater than about pH 10.

18. The process according to claim 2 further comprising the step of: recycling the esterase enzyme or lipase enzyme removed in step (5) into step (2).

19. The process according to claim 2 further comprising the step of: isolating (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol free base in step (5) such that it is substantially free from enzyme protein in step (5).

20. The process according to claim 19 wherein said isolating is performed using a strong base in an excess amount.

21. The process according to claim 20 wherein said strong base is selected from the group consisting of ammonium hydroxide, potassium hydroxide, and sodium hydroxide in water.

22. The process according to claim 4 wherein said free base is converted into said hydrochloride salt by (i) addition of more than one equivalent of hydrochloric acid and a co-solvent or by (ii) addition of more than one equivalent of hydrogen chloride gas and a co-solvent, such that the pH is between about pH 1 to about pH 2.

23. The process according to claim 22 wherein said co-solvent is at least one selected from the group consisting of methanol, ethanol, ethyl acetate, isopropyl acetate, and acetonitrile.

24. The process according to claim 23 further comprising the step of: recrystallizing the (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol hydrochloride salt.

25. The process according to claim 24 wherein said recrystallizing is performed by polishing filtration and crystallization in the presence of at least one organic solvent.

26. The process according to claim 25 wherein said organic solvent is selected from the group consisting of methanol, ethanol, ethyl acetate, isopropyl acetate, acetonitrile, and mixtures thereof.

27. The process according to claim 2 wherein said (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol salt is selected from the group consisting a hydrochloride salt, a hydrogen sulfate, a sulfate salt, a hydrogen phosphate, a phosphate salt, a methanesulfonate salt, p-toluenesulfonate salt, a citrate salt, a fumarate salt, and a tartrate salt.

28. The process according to claim 3 wherein said (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol salt is selected from the group consisting a hydrochloride salt, a hydrogen sulfate, a sulfate salt, a hydrogen phosphate, a phosphate salt, a methanesulfonate salt, p-toluenesulfonate salt, a citrate salt, a fumarate salt, and a tartrate salt.

29. A pharmaceutical composition comprising an active ingredient of (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof prepared in accordance with claim 1 together with at least one pharmaceutically acceptable excipient.

30. A method of treatment of depression, attention deficit hyperactivity disorder, anxiety, obesity, migraine, pain, sexual dysfunction in both men and women, Parkinson's disease, Alzheimer's disease, seasonal affective disorder, addiction to alcohol, addiction to cocaine, or addiction to nicotine-containing products comprising the oral administration to a mammal of an active ingredient comprising (+)-(2S,

3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, prepared in accordance with claim 1 together with at least one pharmaceutically acceptable excipient.

31. The use of (+)-(2S, 3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof prepared in accordance with claim 1 in the manufacture of a medicament.